

B1  
--Figure 1 shows an alignment of the amino acid sequences of MP-52 and MP-121 starting from the first of the seven conserved cysteines with some related proteins. 1a shows the alignment of MP-52 with some members of the BMP protein family (SEQ ID NOS: 22-27); 1b shows the alignment of MP-121 with some members of the Inhibin protein family (SEQ ID NOS: 28-31). \* indicates that the amino acid is the same in all proteins compared; + indicates that the amino acid is the same in at least one of the proteins compared with MP-52 (Fig. 1a) or MP-121 (Fig. 1b).--

Please substitute the second and third paragraphs on page 5 with the following paragraphs:

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--Figure 2 shows the nucleotide sequences of the oligo-nucleotide primer as used in the present invention and an alignment of these sequences with known members of the TGF- $\beta$  family. M means A or C; S means C or G; R means A or G; and K means G or T. 2a depicts the sequence of the primer OD (SEQ ID NOS: 32-42); 2b shows the sequence of the primer OID (SEQ ID NOS: 43-53).

The present invention relates to novel TGF- $\beta$ -like proteins and provides DNA sequences contained in the corresponding genes. Such sequences include nucleotide sequences comprising the sequence

ATGAACTCCATGGACCCCGAGTCCACA (SEQ ID NO: 7) and

CTTCTCAAGGCCAACACAGCTGCAGGCACC (SEQ ID NO: 8)

and in particular sequences as illustrated in SEQ ID NOS: 1 and 2, allelic derivatives of said sequences and DNA sequences degenerated as a result of the genetic code for said sequences. They also include DNA sequences hybridizing under stringent

conditions with the DNA sequences mentioned above and containing the following amino acid sequences:

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cont Met-Asn-Ser-Met-Asp-Pro-Glu-Ser-Thr (SEQ ID NO: 9) or

Leu-Leu-Lys-Ala-Asn-Thr-Ala-Ala-Gly-Thr (SEQ ID NO: 10).

Please replace the first paragraph on page 15 with the following paragraph:

B3  
D3  
~~--The clone was completed to the 3' end of the c-DNA by a method described in~~  
detail by Frohman (Amplifications, published by Perkin-Elmer Corporation, issue 5 (1990), pp 11-15). The same liver mRNA which was used for the isolation of the first fragment of MP-121 was reverse transcribed using a primer consisting of oligo dT (16 residues) linked to an adaptor primer (AGAATTCGCATGCCATGGTCGACGAAGC(T)<sub>16</sub> (SEQ ID NO: 11)). Amplification was performed using the adaptor primer (AGAATTCGCATGCCATGGTCGACG (SEQ ID NO: 12)) and an internal primer (GGCTACGCCATGAACTTCTGCATA (SEQ ID NO: 13)) of the MP-121 sequence. The amplification products were reamplified using a nested internal primer (ACATAGCAGGCATGCCTGGTATTG (SEQ ID NO: 14)) of the MP-121 sequence and the adaptor primer. The reamplification products were cloned after restriction with Sph I in the likewise restricted vector pT7/T3 U19 (Pharmacia) and sequenced with the sequencing kit "Sequenase Version 2.0" (United States Biochemical Corporation). Clones were characterized by their sequence overlap to the 3' end of the known MP-121 sequence.--

Please replace the paragraph bridging pages 17-19 with the following paragraph:

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--The clone was completed to the 3' end according to the above described method (Example 1). The same embryo mRNA, which was used for the isolation of the first fragment of MP-52, was reverse transcribed as in Example 1. Amplification was performed using the adaptor primer (AGAATTCGCATGCCATGGTCGACG (SEQ ID NO: 12)) and an internal primer (CTTGAGTACGAGGCTTTCCACTG (SEQ ID NO: 15)) of the MP-52 sequence. The amplification products were reamplified using a nested adaptor primer (ATTCGCATGCCATGGTCGACGAAG (SEQ ID NO 16)) and a nested internal primer (GGAGCCCACGAATCATGCAGTCA (SEQ ID NO: 17)) of the MP-52 sequence. The reamplification products were cloned after restriction with Nco I in a likewise restricted vector (pUC 19 (Pharmacia #27-4951-01) with an altered multiple cloning site containing a unique Nco I restriction site) and sequenced. Clones were characterized by their sequence overlap to the 3' end of the known MP-52 sequence. Some of these clones contain the last 143 baspairs of the 3' end of the sequence shown in SEQ ID NO: 1 and the 0.56 kb 3' non-translated region (sequence not shown). One of these was used as a probe to screen a human genomic library (Stratagene #946203) by a common method described in detail by Ausubel et al. (Current Protocols in Molecular Biology, published by Greene publishing Associates and Wiley-Interscience (1989)). From  $8 \times 10^5$   $\lambda$  phages one phage ( $\lambda$  2.7.4) which was proved to contain an insert of about 20 kb, was isolated and deposited by the DSM (#7387). This clone contains in addition to the sequence isolated from mRNA by the described amplification methods sequence information further to the 5' end. For sequence analysis a Hind III fragment of about 7.5 kb was subcloned in a likewise restricted vector (Bluescript SK, Stratagene #212206). This plasmid, called SKL 52 (H3) MP12, was also deposited by

the DSM (#7353). Sequence information derived from this clone is shown in SEQ ID NO: 1. At nucleotide No. 1050, the determined cDNA and the respective genomic sequence differ by one basepair (cDNA: G, genomic DNA: A). We assume the genomic sequence to be correct, as it was confirmed also by sequencing of the amplified genomic DNA from embryonic tissue which had been used for the mRNA preparation. The genomic DNA contains an intron of about 2kb between basepairs 332 and 333 of SEQ ID NO: 1. The sequence of the intron is not shown. The correct exon/exon junction was confirmed by sequencing an amplification product derived from cDNA which comprises this region. This sequencing information was obtained by the help of a slightly modified method described in detail by Frohman (Amplifications, published by Perkin-Elmer Corporation, issue 5 (1990), pp 11-15). The same embryo RNA which was used for the isolation of the 3' end of MP-52 was reverse transcribed using an internal primer of the MP-52 sequence oriented in the 5' direction (ACAGCAGGTGGGTGGTGTGGACT (SEQ ID NO: 18)). A polyA tail was appended to the 5' end of the first strand cDNA by using terminal transferase. A two step amplification was performed first by application of a primer consisting of oligo dT and an adaptor primer (AGAATTCGCATGCCATGGTCGACGAAGC (T<sub>16</sub>) (SEQ ID NO: 11)) and secondly an adaptor primer (AGAATTCGCATGCCATGGTCGACG (SEQ ID NO: 12)) and an internal primer (CCAGCAGCCCATCCTTCTCC (SEQ ID NO: 19)) of the MP-52 sequence. The amplification products were reamplified using the same adaptor primer and a nested internal primer (TCCAGGGCACTAATGTCAAACACG (SEQ ID NO: 20)) of the MP-52 sequence. Consecutively the reamplification products were again reamplified using a nested adaptor primer (ATTCGCATGCCATGGTCGACGAAG (SEQ